Clinicopathologic Conference

Fever and Leukopenia in a 2-Year-Old

Moderator
STEPHEN A. SPECTOR, MD

Discussants
CAPT PHILIP GOSCIENSKI, MC, USN; STEPHEN A. SPECTOR, MD; SASKIA HILTON, MD, *and* BETH KLEINER, MD

STEPHEN A. SPECTOR, MD:* *This conference will deviate from the usual Grand Rounds format in that the case to be presented is unknown to the discussant. Dr Beth Kleiner will summarize the findings in this case.*

BETH KLEINER, MD:† This was the first University Hospital admission for this 2-year-old Mexican-American female infant who was admitted because of fever and lethargy.

Report of the Case

The child was well until four days before admission, when a fever to 40°C (axillary) and vomiting developed. Three days before admission she was seen in a medical clinic in Los Angeles where her pharynx was noted to be erythematous and she was treated with intramuscular administration of penicillin. Oral penicillin therapy was also initiated, which was continued daily until admission.

The child's appetite was decreased, but she took fluids well. She continued to have fever and was seen at a community health care center the day before admission. Her pharynx was erythematous and exudates were present. She again was treated with intramuscular administration of penicillin and advised to continue taking oral penicillin.

On the day of admission, the child was seen again at the community clinic. Emesis had stopped, but she began to have diarrheal bowel movements without gross blood. She appeared lethargic and acutely ill and was referred to University Hospital.

The medical history was unremarkable. The child was the normal product of a full-term pregnancy and weighed 3.5 kg at birth. She had grown and developed normally and had no previous medical problems. Her immunizations were up to date. A tuberculin skin test 1½ months before admission was negative. There was no family history of tuberculosis. No family members had recently been ill. The patient lived with her natural parents in San Ysidro; they all frequently visited Mexico.

On physical examination, she was a pale and lethargic child. Her weight was 9.5 kg. The pulse rate was 125 per minute, the blood pressure was 80/60 mm of mercury, the respirations were 22 and the temperature was 40.8°C. The head was normocephalic. There was no conjunctivitis, the sclerae were nonicteric and the fundi were normal. There was no nasal discharge. Tympanic membranes were normal. The mucous membranes were dry; there was a blister on the right dorsal area of the tongue, and her lips were cracked. The pharynx was red, and there was white material on the tongue. The neck was supple; there was some anterior cervical lymphadenopathy. The chest was clear to percussion and auscultation. The heart was normal. The abdomen was soft and bowel sounds were normal. The liver was palpable 1 cm below the right costal margin and the spleen tip was palpable. There were no masses, guarding or tenderness. Rectal examination was negative. Culture of a stool specimen was positive for occult

*Assistant Professor of Pediatrics, Division of Infectious Diseases, University Hospital, San Diego.
†Resident in Pediatrics, University Hospital, San Diego.

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From the Department of Pediatrics, US Naval Regional Medical Center, San Diego, and Departments of Pediatrics and Radiology, University of California Medical Center, San Diego.

Reprint requests to Stephen A. Spector, MD, Division of Infectious Diseases, Department of Pediatrics, University of California San Diego, P.O. Box 3548, H814-G, San Diego, CA 92103.

blood. The extremities were cool. There was no cyanosis, clubbing or edema. The child was extremely lethargic, but her cranial nerves were intact and her reflexes were symmetric.

Laboratory studies disclosed the following values: The serum concentration of glucose was 122, blood urea nitrogen 15 and creatinine 0.6 mg per dl; sodium was 130, potassium 3.4, chloride 96 and bicarbonate 25 mEq per liter. The serum aspartate aminotransferase (formerly SGOT) was 71 IU. The peripheral leukocyte count was 3,400 per cu mm with 41 percent polymorphonuclear leukocytes, 38 percent band forms, 18 percent lymphocytes, 2 percent monocytes and 1 percent metamyelocytes. The hemoglobin level was 10.3 grams per dl and the hematocrit 30 percent. The platelet count was 70,000 per cu mm. Urine analysis showed a specific gravity of 1.025, a pH of 5.5, 2+ protein and two to five leukocytes per high power field. The cerebrospinal fluid contained one lymphocyte, no erythrocytes, protein level of 7.0 and glucose level of 67 mg per dl. Gram stain was negative for bacteria. A roentgenogram of the chest showed no abnormalities. An abdominal film showed slightly dilated loops of bowel with no masses and no free air.

An electroencephalogram showed generalized slowing. The patient remained febrile to 39°C and was profoundly lethargic. A repeat blood count showed a leukocyte count of 1,700 per cu mm with 13 percent polymorphonuclear leukocytes, 23 percent band forms, 54 percent lymphocytes, 9 percent monocytes and 1 percent metamyelocytes. The hemoglobin level fell to 8.3 grams per dl. The reticulocyte count was 0.1 percent and the platelet count fell to 24,000 per cu mm. The prothrombin time, partial thromboplastin time and fibrinogen in the serum remained normal. Treatment with administration of ampicillin and chloramphenicol was continued. Bone marrow aspiration on the second day showed decreased cellularity and decreased numbers of megakaryocytes. Myeloid maturation was normal. An abdominal ultrasound examination showed mild hepatosplenomegaly and a small amount of free peritoneal fluid. A contrast roentgenographic study was carried out.

DR SPECTOR: *The roentgenographic findings will be presented by Dr Hilton.*

SASKIA HILTON, MD:* Before I present the findings of the roentgenographic studies, let me summarize the problem with which we were presented. A 2-year-old female infant was febrile and had a history of vomiting. Although her stool was not frankly bloody, it had been positive for occult blood. She had no evidence of an abdominal mass, but on ultrasound was found to have peritoneal fluid. The clinical impression was that she had colitis, but it was necessary to rule out the possibility of a surgical lesion, specifically, appendicitis or intussusception. The barium enema study was done, therefore, not to evaluate a possible colitis, but to exclude a surgically correctable illness.

*Assistant Professor of Radiology, University Hospital, San Diego.

Roentgenographic Findings

The plain roentgenographs showed multiple loops of mildly dilated bowel. Cross-table views confirmed that there was no free intraperitoneal air, indicating that perforation of the bowel had not occurred and that the patient did not have a toxic megacolon.

The barium enema study showed a normal colon with the exception of the ascending segment. An intussusception was not present and the appendix was normal. The rectum was normal and without spasm, thereby excluding congenital megacolon (Hirschsprung's disease). The ascending colon showed pronounced mucosal edema, which could be seen as apparent mucosal masses projecting into the bowel lumen. No ulcerations were present.

In summary, there was mucosal edema in the ascending portion of the colon. The differential diagnosis included colitis of any etiology, hemolytic uremic syndrome, Schönlein-Henoch purpura or submucosal bleeding in a hemophiliac patient. The most likely diagnosis was colitis. A surgical lesion had been excluded.

DR SPECTOR: *The case will be discussed by Dr Philip Goscienski.*

CAPT PHILIP GOSCIENSKI, MC, USN:† In undertaking a conference in which the format is that of a clinicopathologic conference, the discussant has two objectives: one is to make the correct diagnosis, and the second is to make it a worthwhile teaching exercise.

Discussion

It is certainly important to make a correct diagnosis in a patient as ill as this child. This 2-year-old girl had a four-day history of high fever and vomiting. Her symptoms did not improve after she was given penicillin. Instead, she continued to have a high fever, becoming somewhat dehydrated and lethargic. The findings of the physical examination were not consistent with the history that her growth had been normal. At 24 months of age, I would have expected her to be a little heavier than 10 kg (23 lb), which would have been her rehydrated weight. The lethargy mentioned in the history I have considered a strong clue. The fact that meningism was not described does not assure me that it was not present, but I must assume that to be the case. I accept the finding that the cranial nerve examination was also normal. She was dehydrated and had an inflamed pharynx. The pulse rate was not very high in view of the apparent severity of her illness. One wonders if there was contact with animals, or if there was any particular reason why a tuberculin skin test was done a few weeks before this present illness. If she was not entirely well until four days before admission, as the history told us, there must have been a preceding illness that might have indicated the need for a tuberculin skin test.

Her hematologic findings were interesting. On admission, she had leukopenia but did not have a neutro-

†US Naval Regional Medical Center, San Diego.

penia. The absolute neutrophil count was over 2,600 per cu mm, which is normal. It then declined to about 1,000 and that could be an ominous or a benign finding. The leukocyte count can only suggest or support a diagnosis. It rarely helps us to make a specific diagnosis. I believe it was helpful but not definitive in this instance.

The normal findings on the lumbar puncture study must have been reassuring to the attending physician. The likelihood of there being meningitis or encephalitis in the presence of such a normal spinal fluid is very remote. The changes in her bone marrow were considerable; all of the elements were decreased. We do not know if she had taken chloramphenicol before admission, but I do not believe chloramphenicol toxicity contributed to this child's illness. Idiosyncratic marrow aplasia usually does not occur until two weeks or more after stopping therapy. The expected pharmacologic-hematologic changes are seldom as dramatic as those that occurred in this patient. Platelet counts rarely drop below 100,000 per cu mm and neutropenia tends not to be seen. There is an increase in the myeloid-erythroid ratio and some vacuolization of the marrow precursors, especially erythrocyte precursors. I prefer, therefore, to think that her hematologic changes occurred due to the infectious process.

The finding of a small amount of free peritoneal fluid is a tantalizing one. I wonder how far along in the course that first occurred. The dilation of the bowel noted could have represented only a mild paralytic ileus, but there is the possibility in an infant this age of an intermittent intussusception that may produce some changes, even a fairly toxic appearance at times.

The differential diagnosis in this case is long. There are relatively few entities, however, that are really good candidates to explain this child's illness. I will attempt to discuss this case as most of us would have thought it out, rejecting some diagnoses and adding others as the clinical features emerge.

A diagnosis of tuberculous meningitis in a lethargic 2-year-old must be considered, but is unlikely in a patient with these findings in the cerebrospinal fluid. Our service handles several patients yearly with tuberculous meningitis and needs always to be alert to this diagnosis. How likely is tuberculous meningitis in this patient? A negative family history is a big help, but why did she have a skin test six weeks earlier? Was there a neighborhood contact, or perhaps a babysitter or a relative from across the border? A negative tuberculin skin test really tells us very little. About half of our patients with tuberculous meningitis are skin-test negative at the time of admission. About the same can be said of the chest radiograph. Almost half of the patients with tuberculous meningitis show no radiographic evidence of pulmonary disease.[1] How about the cerebrospinal fluid? In patients with tuberculous meningitis, the cerebrospinal fluid cell count may be normal or the protein level may be normal, but it would be extremely unlikely that both would be normal in a patient with enough disease to have the symptoms she has. The historical and physical findings also lead us away from a diagnosis of tuberculous meningitis. There was no contact with persons with tuberculosis; apparent good health until four days before admission, high fever, the absence of cranial nerve findings and the absence of meningeal signs are all against it.

There is a southwestern United States disease that sometimes resembles tuberculous meningitis, and that is meningitis due to *Coccidioides immitis*. It tends to be less acute than this particular patient's illness, and the cerebrospinal fluid findings made this an extraordinarily unlikely diagnosis. Certainly any ill child may have bacterial meningitis and, despite no meningeal symptoms, it was still a possibility. However, I feel it was adequately ruled out by the normal findings from the lumbar puncture. I urge you to remember that the spinal fluid can change in a very short time; I have seen spinal fluid changes occur in a matter of six to eight hours, going from almost no cells (certainly fewer than ten mononuclear cells) to several hundred neutrophils in a relatively short period of time.

A high fever with lethargy and a red throat, no response to penicillin therapy and a "viral" leukocyte count all make a tempting case for infection with an Epstein-Barr virus. There are absolutely no diagnostic features of Epstein-Barr virus infection in small children. The mononucleosis spot test is often negative; Epstein-Barr titers are not immediately available, and atypical lymphocytes and excessive numbers of monocytes may not be present in a peripheral blood smear. In any case, a toxic-appearing, cold, clammy 2-year-old infant is not a likely candidate for Epstein-Barr virus infection unless there is some accompanying complication. In the same vein, cytomegalovirus and herpes simplex virus, though they too can produce diseases with severe and protean manifestations, are poor candidates in this particular case. When herpes simplex virus causes central nervous system disease, it leaves an identifiable trail, usually in the form of leukocytes, erythrocytes and some protein in the spinal fluid, and frequently some focal neurologic findings. Cytomegalovirus does not usually cause significant clinical illness in an otherwise healthy 2-year-old.

Shigella infection sometimes makes children quite ill. It is by no means rare for a patient to have profound fever, some vomiting and lethargy, even seizures, before the onset of diarrhea. Sooner or later there will be diarrhea, generally more serious than that described in this patient. *Shigella* may also produce some striking hematologic changes, from leukopenia to leukemoid reaction. A raised band count is fairly common, but it tends to be higher than it was in this patient. Other elements of the blood are not usually affected. When a *Shigella* infection is due to a particular serotype, *dysenteriae,* type 1, the symptoms may be more severe than the ordinary case of shigellosis. There may be a toxic megacolon. These patients sometimes have all the features of severe, acute ulcerative colitis with shock and renal shutdown. Some of these patients undergo total colectomy in the mistaken idea that they have

toxic megacolon due to ulcerative colitis. This patient did not appear to be that ill. Her abdominal findings did not seem to reveal that much illness.

I tend to lean toward a diagnosis of bacterial sepsis in this patient. There was no obvious focus. Her lethargy, cold, clammy appearance, relative hypotension and poor capillary filling suggested that antibiotic treatment should be initiated as soon as cultures were done. She was obviously also in need of fluid replacement, as indicated by many physical signs of dehydration.

A 2-year-old with high fever and leukocytosis is a good candidate for bacteremia due to the pneumococcus or *Hemophilus influenzae,* type b. This child did not have a leukocytosis; she had leukopenia, though as I mentioned earlier, she did not have neutropenia. If that blister on her tongue had been on the surface of the gingiva or hard palate, I would have considered pneumococcal bacteremia. There have been some case reports of pneumococcal bacteremia in which the patient had a bullous lesion of the mucosa either on the surface of the gingiva or on the hard palate.[2] As far as I know, in only one of those patients has there been histologic and bacteriologic examination of the lesion, and no organisms were seen there. However, I do not think that this patient had sepsis due to pneumococcus or *H influenzae.*

Neisseria meningitidis sepsis tends to be a fulminating process. It is generally accompanied by skin lesions that are virtually pathognomonic. Neutropenia is not only a common accompaniment of meningococcal sepsis, but it is also a poor prognostic sign. Meningitis may not be present. In fact, the absence of meningitis is also a poor prognostic sign in meningococcemia.[3]

A relative newcomer is *Yersinia enterocolitica.* Only in the past few years has this organism received attention in the medical literature. It does cause sepsis at times, but it more often causes an ileitis and mesenteric adenitis, with or without diarrhea.[4] That could explain her peritoneal fluid seen on ultrasound study. A history of animal contacts would have been helpful. There have been two family outbreaks of serious disease due to *Y enterocolitica* associated with household dogs.

In the Southwest, another *Yersinia, Yersinia pestis,* the plague bacillus, must also be considered in the differential diagnosis of what appears to be sepsis. *Y pestis* may be transmitted by dogs and cats, and there is no need for an insect vector.[5] Against the possibility of plague septicemia in this case is the absence of pneumonia, which is likely to be present if there is no vector. Even though I do not think this child had sepsis due to *Y pestis,* it is always an important disease to consider, particularly in California.

What impressed me most about this child was the triad of lethargy, high fever and leukopenia. My diagnosis then was sepsis, and the lethargy or the stupor that occurred in this patient is the symptom on which I would base my diagnosis. The Greek word for stupor is *typhos,* and the diseases typhus and typhoid (which means "typhos-like") are similar enough so that they were not clearly differentiated from one another until about 150 years ago, even though they both wreaked havoc on humanity for hundreds, perhaps thousands, of years. Typhus has disappeared from this country; typhoid has not. It will continue to occur in any population whose way of life includes poor sanitation. It has been said a number of times that the relative disappearance of typhoid from the United States could be attributed to the plumbers of our country rather than to the physicians.

What supports the diagnosis of typhoid in this patient? In addition to the fever and lethargy, she had several of the findings noted in children with this disease—vomiting, mild diarrhea, a relatively normal pulse rate, an erythematous pharynx, mild splenomegaly and guaiac-positive stools. That all sounds consistent with a viral illness but the changes in sensorium and the hematologic changes point toward a more serious diagnosis. It would have been nice to know if rose spots had developed. Many patients with typhoid have rose spots, but they may not appear until about the second week of illness, when a convalescing, afebrile patient may not be examined daily. Rose spots may be very few in number, perhaps fewer than ten, and a physician who has never seen one may not recognize them. If a patient's skin is fairly dark, rose spots may be practically invisible.

Febrile agglutinin titers are practically worthless in the diagnosis of an acute illness. They may be negative at the acute stage, and some patients may have a positive titer due to past infection or immunization. Not only are several days required for a diagnostic fourfold titer, but in some patients with untreated typhoid a rise in febrile agglutinins never occurs.[6]

In 1937 Harry Dietrich[7] summarized the findings in 60 children with typhoid at Los Angeles Children's Hospital. The youngest patient was 21 days old. Symptoms were frustratingly nonpathognomonic: fever, abdominal pain, vomiting, headache, malaise, drowsiness, diarrhea, constipation and delirium. They occurred in 20 percent or more of the patients. But none of the patients had all of these symptoms, and some patients had no fever. Central nervous system symptoms were prominent and included intractable irritability, stupor and coma.

Physical findings were not much help either. Most patients had rose spots, but not until late in their disease. Many had hepatosplenomegaly, though 25 percent did not. Falling leukocyte counts were common, but no patients in that group had a bone marrow examination. Absence of diarrhea does not rule out typhoid fever; constipation is common. Stool cultures are often negative until the end of the third week of illness, but in 85 percent they were eventually positive in that 1937 study.

Of course, in 1937 none of those patients received antibiotics. They remained febrile from one to seven weeks. Some of the fevers were sustained; some were irregular. Three patients died, one of probable Gram-

negative shock, one of staphylococcal sepsis and one with combined problems of cerebral edema and myocarditis.

Almost 30 years after Dietrich's paper, a report appeared of a typhoid epidemic in Scotland.[8] There were 507 patients, 86 of them children. These were of middle- and upper-class families in Aberdeen whose infection came from the meat counter of a supermarket. The fact that this was a healthy population that received early treatment is an important factor, and might well explain why that epidemic was so benign; there were no deaths among the 86 children. Again, as in 1937, typhoid was a nonspecific illness. The symptoms were mild but keep in mind that those patients were identified by positive stool cultures and some of them (15 of 86) were entirely asymptomatic.

In the treatment of typhoid, ampicillin and chloramphenicol are both effective agents, but patients treated with chloramphenicol may have a higher relapse rate.[9] For example, in the early 1970s, there was an outbreak of typhoid in a Florida migrant labor camp.[10] More than 100 children were treated with chloramphenicol. The relapse rate was 6.8 percent, but there were no relapses in those patients receiving ampicillin. About ten years ago an epidemic of typhoid fever began in Guatemala and spread to Central Mexico.[11] The organism was resistant to chloramphenicol but was sensitive to ampicillin. I would suggest that anyone in Southern California suspected of having typhoid, especially a toxic-appearing patient, be given antibiotics or ampicillin alone unless the sensitivity pattern is known. Trimethoprim-sulfamethoxazole therapy has been tried in typhoid with fairly good clinical results, but relapse rates may be higher than with chloramphenicol.[12]

In summary, I believe that this 2-year-old had typhoid fever, with marrow depression due to that disease. I suspect that *Salmonella typhosa* is the particular causative organism, but other *Salmonella* sps cause a typhoid-like syndrome that is indistinguishable from mild typhoid.

DR SPECTOR: *Thank you, Dr Goscienski.*

Summary

On the second hospital day, six to ten discrete papular erythematous lesions developed that were confined to the anterior chest and abdomen. These lesions initially blanched, but faded rapidly and were gone the following day. They had all the features of the rose spots found in typhoid fever. Cultures of specimens of the patient's blood and stool subsequently grew *S typhosa.*

Recently the Center for Disease Control reviewed reports of *Salmonella* bacteremia from 1968 through 1979.[13] During that 12-year period there were 8,018 organisms of 128 serotypes identified. California recorded the highest numbers of *Salmonella* organisms found in blood of any state, comprising 18 percent of the total. Six serotypes of *Salmonella* accounted for nearly 70 percent of organisms found in blood, with *S typhosa* accounting for 23.4 percent; *Salmonella typhimurium,* 20.3 percent; *Salmonella enteritidis,* 10.2 percent; *Salmonella heidelberg,* 8.9 percent; *Salmonella choleraesuis,* 3.8 percent, and *Salmonella saint-paul,* 2.6 percent. The reported identification rate in blood per million people was highest for infants younger than 1 year of age, with the peak rate in the 1-day to 2-months-old group. The incidence for 2-year-olds was about 50 per 100,000 population.

S typhosa, S enteritidis, serotype *paratyphi* A and serotype *paratyphi* B infect only humans. The incidence of typhoid fever is determined, therefore, by the prevalence of human carriers, the adequacy of environmental sanitation and the purity of the water supply. Technical improvements in handling human wastes and water have more than any other factors decreased the incidence of typhoid fever. In underdeveloped countries, however, where there is poor sanitation and contamination of water supplies, typhoid fever remains a common endemic illness.

The fact that *S typhosa* infects only humans theoretically should facilitate efforts to eliminate typhoid fever. Vaccines of killed typhoid organisms have been used since the late 19th century, though their efficacy was not established until the 1960s. Field trials in Guyana showed that the heat-, phenol- and acetone-inactivated vaccines are 65 percent to 90 percent effective in preventing typhoid fever.[14] Although typhoid fever usually confers lifelong immunity, the nature of protection is unknown. The titers of antibodies against O, H and Vi antigens have not been connected with protection. Naturally occurring sources of *S typhosa* usually contain 100,000 organisms. Volunteer studies indicate, however, that vaccine-acquired immunity can be easily overcome with a challenge of 50 percent infectious dose (10 million) of *S typhosa* organisms.[15] The effectiveness of *paratyphi* A and B vaccines has never been established, and they are not recommended for use either individually or in combination with typhoid vaccine. Typhoid vaccine in the United States is not recommended for general use, and is not indicated for controlling common source outbreaks or in natural disasters.[16]

As Dr Goscienski said, there are three drugs—ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole—that favorably influence the outcome of typhoid fever. This child was treated with both ampicillin and chloramphenicol and recovered rapidly. On follow-up examinations, she had no evidence of relapse.

PHYSICIAN IN THE AUDIENCE: *Can you comment on the thrombocytopenia observed in this patient?*

DR SPECTOR: Abnormalities of clotting studies, including thrombocytopenia, hypofibrinogenemia and increased levels of circulating fibrin-split products, have been reported in over 50 percent of patients with typhoid fever. This patient's platelet count fell to 24,000 per cu mm on the second day of hospital stay. While receiving

adequate antibiotic therapy, her platelet count rose to over 100,000 per cu mm by the fourth day of hospital stay.

PHYSICIAN IN THE AUDIENCE: *How common is pharyngitis with typhoid fever?*

DR SPECTOR: Pharyngitis is well described in association with typhoid fever. The reported incidence, however, is quite variable. In the preantibiotic era, in one large study more than 10 percent of patients had sore throats associated with typhoid fever. In a recent outbreak of typhoid fever, only 5 percent of patients had a sore throat. It is important to remember that the initial clinical manifestations of typhoid fever in children as well as adults frequently mimic an upper respiratory tract infection. Fever, headache, cough and cervical adenopathy, as well as pharyngitis, are common. Respiratory findings including rales on auscultation are frequently present.

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